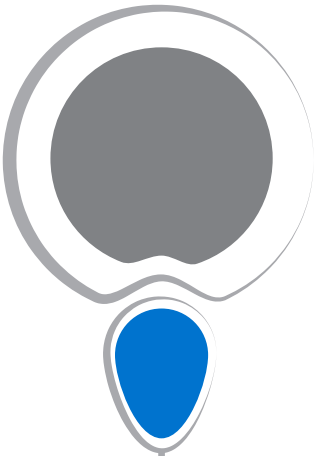


Reproductive Endocrinology and Infertility

Handbook for Clinicians

2nd Edition

Dan I. Lebovic, MD
Professor
Department of Obstetrics and Gynecology
University of Wisconsin School of Medicine
Madison, WI

John David Gordon, MD
Co-Director, Dominion Fertility, Arlington, VA
Clinical Professor, Obstetrics and Gynecology
The George Washington University School of Medicine
Division Director, Reproductive Endocrinology and Infertility
Inova Fairfax Hospital

Robert N. Taylor, MD, PhD
Professor
Department of Obstetrics and Gynecology
Wake Forest School of Medicine
Winston-Salem, NC

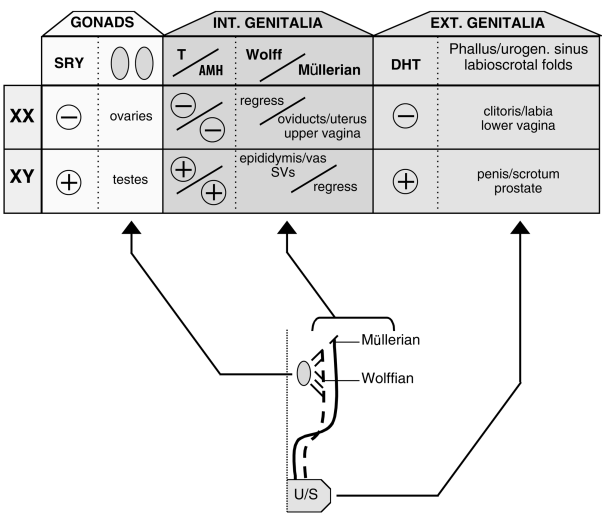
Contents

1

Sexual Differentiation: From Gonad to Phallus

EMBRYOLOGY

- Bipotential: gonads and external genitalia (urogenital sinus; two labioscrotal swellings; genital tubercle)
- Unipotential: wolffian or müllerian ducts



T, testosterone
AMH, anti-müllerian hormone
SVs, seminal vesicles
DHT, dihydrotestosterone
SRY, sex-determing region of the Y-chromosome
U/S, urogenital sinus

2
Puberty

DEFINITION

- Puberty is the process of biologic and physical development through which sexual reproduction first becomes possible.
- Progression:
  - thelarche → adrenarche → peak growth spurt → menarche → ovulation

FACTORS AFFECTING TIME OF ONSET

- Genetics (average interval between menarche in monozygotic twins is 2.2 months compared with 8.2 months in dizygotic twins) (McDonough 1998)
- Race: African-American girls enter puberty 1.0–1.5 years before white girls (Herman-Giddens 1997)
- Nutritional status: earlier with moderate obesity; delayed with malnutrition
- General health
- Geographic location: urban, closer to the equator, lower altitudes earlier than rural, farther from the equator, higher altitudes
- Exposure to light: blind earlier than sighted
- Psychological state
- Several pathologic states influence the timing of puberty either directly or indirectly, contributing to a gaussian distribution (Palmert 2001).

3

Pediatric and Adolescent Gynecology

PEDIATRIC GYNECOLOGY

Physical Examination Specifics

- Weight and height → assess appropriate growth
- Breast examination → Tanner staging (see Chapter 2, Puberty, for diagram)
- External genitalia

Examination	Notes
Positioning	Frog-legged, knee-chest position (if girl takes a deep breath may actually see the cervix), mother on examination table with child, or child on mother's lap.
Pubic hair	Tanner staging (see Chapter 2, Puberty, for diagram).
Clitoris	Normal is ~3 mm × 3 mm.
Signs of estrogenization	Mucosal tissues in premenarchal child are thin and red.
Perineum	Look for hygiene.
Type of hymen	Crescent or posterior rim, annular, fimbriated or redundant, imperforate, microperforate, cribriform, septate.
Size of hymen opening	Upper limit of normal is 1 mm for each year of age, although controversy exists on method of measurement; standard → perform in prone knee-chest position with gentle traction on labia.
Vagina	Examine under anesthesia if more visualization of the vagina is needed; this allows for vaginoscopy, cultures, and biopsies as indicated.

4
Müllerian Agenesis

SYNONYMS

- Müllerian agenesis (MA)
- Mayer-Rokitansky-Küster-Hauser syndrome
- Vaginal agenesis

DEFINITION

- 46,XX with normal, functioning ovaries; lack of fallopian tubes, uterus, and upper vagina

INCIDENCE

- 1 in 5,000 to 7,000

ANATOMY *(Griffin 1976)*

- Normal external female genitalia
- Normal ovarian function; thus, normal female secondary sexual characteristics
- Absence of fallopian tubes, uterus, internal vagina → some variations in degree of müllerian structure regression; 5% have a uterus
- ⅓ of MA patients have renal anomalies (renal agenesis, malrotations, ectopic kidneys)
- Possible spinal and skeletal anomalies
- Patients usually present with primary amenorrhea; need to differentiate from those with imperforate hymen, transverse vaginal septum, or complete androgen insensitivity syndrome

5
Septate Uterus

BACKGROUND

- Congenital uterine anomalies resulting from müllerian fusion defects are the most common types of malformations of the reproductive system (Rock and Jones 1977).
- Mechanism of pregnancy loss: implantation into a poorly vascularized, fibrous septum (Fedele 1996b)
- Bicornuate uterus is not generally associated with RPL (Proctor and Haney 2003).

PREVALENCE

Prevalence (%) of Uterine Anomalies:

	General Population	Subfertile	RPL (≥3 losses)
Arcuate	3.9	1.8	6.6
Septate	**2.3**	**3**	**15.4**[a]
Bicornuate	0.4	1.1	4.7[b]
TOTAL (all types of anomalies)	5.5	8	24.5

[a] May have classified arcuate as a diagnosis of septate.
[b] May have classified septate as a diagnosis of bicornuate.
Adapted from Chan YY, Jayaprakasan K, Zamora J et al. The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. *Hum Repod Update* 17(6):761-771, 2011.

- The incidence of endometriosis was found to be higher in women with a septate uterus compared to without (~26% vs. 15%) (Nawroth 2006)

EMBRYOLOGY

- Müllerian ducts develop by in-folding of the coelomic epithelium overlying the *urogenital ridge*, and, in the absence

6
Turner Syndrome

DEFINITION AND PREVALENCE
(Ranke and Saenger 2001)

- Turner syndrome (TS; also known as *Ulrich-Turner syndrome*): combination of characteristic physical features (short stature and gonadal dysgenesis) and complete or partial absence of 2nd X chromosome
- 1 in 2,000 live births
- 1% of 45,X fetuses survive to term
- 10% of spontaneous losses have 45,X karyotype (most common aneuploid in 1st trimester [TM] loss)
- *Not* associated with advanced maternal or paternal age
- http://www.turnersyndrome.org

DIAGNOSIS *(Ranke 2001)*

- *Ultrasound findings:* ↑ nuchal translucency, cystic hygroma, coarctation of aorta ± left-sided cardiac defects, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, growth retardation
- *Karyotype (chorionic villus sampling [CVS]/amniocentesis):* necessary for diagnosis (confirm postnatally, if clinical suspicion is high and peripheral blood karyotype normal, then 2nd tissue should be checked)
- *Potential mosaic karyotypes:* 45,X/46,XX; 45,X/46,XY (mixed gonadal dysgenesis); 45,X/46,XX; 45,X/46,Xxiq (phenotype, including stature, impossible to predict with mosaics, although there is clearly a ↓ fertility rate with ↑ risk of spontaneous loss and premature ovarian failure)
  - Spontaneous menses have been reported in ~40% of 45,X/46,XX vs. only 2–10% of those with 45,X. FSH ought to be tested and repeated yearly to follow gonadal function longitudinally in mosaic individuals (Fechner 2006)

7
Menstrual Cycle

CHARACTERISTICS OF THE NORMAL MENSTRUAL CYCLE

- Purpose: renewal of uterine lining to optimize embryonic implantation
- Mechanism: closely coordinated interactions between the hypothalamus, pituitary gland, and ovaries producing cyclic changes in target tissues of the reproductive tract → endometrium, cervix, and vagina
- Fast facts:
  - Mean age of **menarche** = **12.8 years old**; mean age of menopause = **51 years old**
  - Cycle day 1 = first day of vaginal bleeding; mean duration of flow = 4 ± 2 days
  - Cycle length:
    - ➔ Least variable between ages 20 and 40 years (gradual decrease in length)
    - ➔ 90% have menstrual cycles between **24 and 35 days;** 15% have 28-day cycles.
  - Irregular cycles: **just after menarche** (2 years); **just before menopause** (3 years)
  - Menstrual cycle phases:
    - ➔ **Follicular phase**: variable length (7–21 days); key determinant of cycle length
    - ➔ **Ovulation**
    - ➔ **Luteal phase**: **more constant** (≥12 days)
- Mitotic division of germ cells ceases by the 7th month of fetal life, although there are data indicating the presence of germline stem cells allowing follicular renewal in the postnatal ovary (Johnson 2004a; Tilly 2012).

8

Abnormal Uterine Bleeding

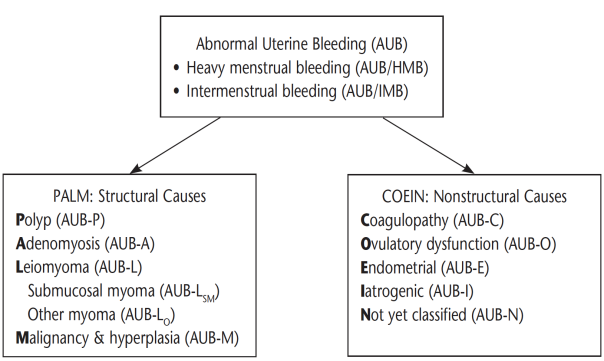
DEFINITION

- Abnormal menstrual volume, duration, regularity, or frequency.

CLASSIC TERMINOLOGY

Term	Menses Pattern
Oligomenorrhea	>35-day cycle length
Polymenorrhea	<21-day cycle length
Menorrhagia	↑ Flow (>80mL blood loss) or duration at regular intervals
Metrorrhagia	Bleeding between periods
Menometrorrhagia	↑ Flow or irregular intervals

PROPOSED NEWER TERMINOLOGY



Source: Reproduced with permission from Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Committee Opinion No. 557. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 121:891–6, 2013.

9

Oral Contraceptives

STEROID COMPONENTS OF ORAL CONTRACEPTIVES

Estrogen Component

- Peak serum levels in 1.2–1.7 hours
- **Estradiol (E_2)** is the most potent natural estrogen (E) and the major E secreted by the ovaries. An ethinyl group at the C-17 position makes E_2 orally active. All current oral contraceptives (OCs) use ethinyl estradiol (EE), estradiol valerate or mestranol.
- Physiologic effects:
  - Potentiates the action of the progestogenic component by ↑ progesterone (P_4) receptors
  - Stabilizes the endometrium to minimize breakthrough bleeding (BTB) and irregular shedding

Progestin Component

- Peak serum levels in 2 hours

Synthetic Progestins

- Physiologic effects:
  - Contraception but not an absolute anovulatory effect (with current lower EE doses)
    - ➔ Ovulation still occurs in approximately 3% of cycles (Teichmann 1995).
  - Turbidity of cervical mucus
  - Inhibit *spinnbarkeit*
  - Suppression of endometrial gland maturation → decidualized

10
Amenorrhea

DEFINITION

- No menses by age 14 in absence of 2° sexual characteristics (primary)
- No menses by age 16 despite 2° sexual characteristics (primary)
- No menses in 3 cycles or 6 months (secondary)

PHYSIOLOGIC AMENORRHEA

- Prepubertal (menarche range, 9–17 years old)
- During lactation and pregnancy
  - When amenorrhea is present in a woman of childbearing age, must first rule out pregnancy
- Postmenopausal

ETIOLOGY

Primary

- 43% Gonadal failure
- 14% Congenital absence of the vagina
- 10% Constitutional delay

Secondary

- 39% Chronic anovulation
- 20% Hypothyroidism/hyperprolactinemia
- 16% Weight loss/anorexia

DIAGNOSTIC ALGORITHM FOR AMENORRHEA *(see algorithms in the appendices)*

- Majority of cases accounted for by polycystic ovary syndrome (PCOS), hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure.

12
Ectopic Pregnancy

INCIDENCE *(Lipscomb 2000)*

- 2% of pregnancies (1992); 9% of pregnancy-related deaths (5/10,000)
- Recurrence risk: approximately 15%

ETIOLOGY

- Tubal disease
  - In histologic sections of ectopic sites, there was a 45% incidence of pelvic inflammatory disease.
- Gonadotropin therapy
- Ratio of ectopic pregnancies (EPs) to all pregnancies:
  - All women—1:50
  - Copper intrauterine device (IUD)—1:16
  - Levonorgestrel IUD—1:2

DIAGNOSIS *(extrauterine pregnancy)*

- Signs and symptoms of eccyesis: severe abdominal pain (90%), vaginal spotting (80%), amenorrhea (80%), pelvic mass on examination (50%) (Pisarska 1998)
- Most common location: ampullary region of tube (80%), isthmic (12%), fimbria (6%)

Human Chorionic Gonadotropin

- 0.79 mIU human chorionic gonadotropin (hCG) per cell per day approximately 2 weeks after fertilization (Braunstein 1973)
- hCG produced 8–9 days after ovulation by cytotrophoblasts (for corpus luteum rescue)
- βhCG normally 100 mIU/mL at time of missed menses

13
Sheehan Syndrome

INCIDENCE

- 1/10,000 deliveries
- Hemorrhagic infarction usually occurs in the presence of a pituitary tumor.
- Ischemic infarction may occur after obstetric hemorrhage (Sheehan syndrome).

DEFINITIONS

- Postpartum pituitary necrosis is preceded by a history of massive obstetric hemorrhage, resulting in severe circulatory collapse, hypotension, and shock.
- Clinical manifestations may range from partial deficiency to panhypopituitarism (PRL, GH, LH, FSH, ACTH, TSH).
- The posterior pituitary is usually spared.
- Return of normal fertility has been documented.

ETIOLOGY

- Anterior pituitary grows during pregnancy due to estrogenic stimulation, resulting in hyperplasia and hypertrophy of pituitary lactotropes: 500 mg → 1,000 mg.
- Anterior pituitary insufficiency occurs when >75% of the gland has been destroyed.
- Severity of hemorrhage and occurrence of Sheehan syndrome may not correlate.
- Severe hypotension, in a setting of low portal vein pressure, leads to occlusive spasm of the arteries that supply the anterior pituitary and the stalk; when arteriospasm relaxes, blood flows into the damaged vessels, resulting in vascular congestion and thrombosis.

14
Premenstrual Syndrome

HISTORY

- Dr. Frank at Mt. Sinai Hospital in New York City first defined premenstrual syndrome (PMS) in 1931 as a "Feeling of indescribable tension from 10 to 7 days preceding menstruation which in most instances continues until the time that the menstrual flow occurs" (Frank 1931).
- Drs. Greene and Dalton first used the phrase *premenstrual syndrome* in 1953 in a report of 84 cases (Greene and Dalton 1953).

DEFINITIONS

- **PMS:** both physical and behavioral symptoms that occur repetitively in the 2nd ½ of the menstrual cycle to interfere with a woman's life followed by a period of time free of symptoms.
- **Premenstrual dysphoric disorder (PMDD):** American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (*DSM-V*), designation with prominence of anger, irritability, and internal tension; presumably the most severe form of PMS, although this designation is nonfunctional.

PREVALENCE *(Rivera-Tovar and Frank 1990; Raja 1992)*

- Mild PMS: up to 80% in women with regular cycles, moderate to severe PMS affects 20–40% and severe PMDD affects 3–8%
- No correlation with ethnicity
- Higher concordance rate in monozygotic twins compared with dizygotic twins (Condon 1993), although role of genetic factors is far from certain (Glick 1993)

15
Chronic Pelvic Pain

DEFINITION

ACOG: Non-cyclic pain of 6 or more months duration that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks and is of sufficient severity to cause functional disability or lead to medical disability

INCIDENCE

- Affects 15% of women in the United States (9 million)
- Accounts for 10% of gynecologist visits
- Accounts for 40% of laparoscopies
- Accounts for ~12% of hysterectomies

HISTORY

- Menses with dysmenorrhea
- Dyspareunia (superficial suggests inflammatory process or introital muscle control; deep suggests endometriosis or pelvic adhesive disease)
- Sexually transmitted infections (STIs); abnormal Pap smear
- Obstetric history
- Detailed social and family history
- Gastrointestinal (GI), urologic, and musculoskeletal review of symptoms (ROS)
- Past surgical history (abdominal or pelvic) → review old operative reports
- Past and current state of mental health
- History of sexual abuse; depression

Pain Inquiry

- Character
- Radiation

16
Endometriosis

DEFINITION

- Presence of functioning endometrial glands and stroma outside the usual location of the uterine cavity
- First described in 1860 by the Viennese pathologist Karl von Rokitansky
- Visual inspection at the time of laparoscopy is sufficient; in fact, negative histology does not exclude a diagnosis of endometriosis (Kennedy 2005).

PREVALENCE

- 11% of reproductive-age group
- 25–35% of infertile women
- 70% of women with pelvic pain
- Average age at diagnosis: 25–29 years; similar rates in the various races and socioeconomic backgrounds
- 7 million U.S. women are affected.
- Visualizing endometriosis:
  - 70% of women with pelvic pain (Koninckx 1991)
  - 84% of women with pain and infertility (Koninckx 1991)
  - 45% of women with no symptoms (Balasch 1996)
  - 6% of biopsies of normal peritoneum in normal pelvis show microscopic lesions (Balasch 1996)
  - 11–25% of biopsies of normal peritoneum in endometriosis patients (Murphy 1986; Balasch 1996)

17
Fibroids

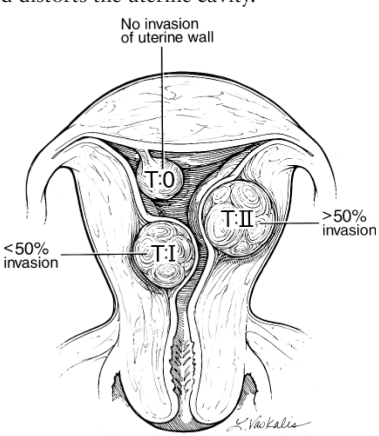
PREVALENCE

- Cumulative incidence of fibroids by age 50 of 70–80% (Baird 2003)
- 70–80% cumulative incidence of fibroids at 50 yo.
- Prevalence of uterine myomas in the 1st trimester of pregnancy (prospective cohort study) (Laughlin 2009):
  - **18% in African-American women**
  - **10% in Hispanic women**
  - **8% in white women**

CLASSIFICATION

Submucosal

- Fibroid distorts the uterine cavity.



Source: Reproduced with permission from Cohen L, Valle R. Role of vaginal sonography and hysterosonography in the endoscopic treatment of uterine myomas. *Fertil Steril* 73(2):197–204, 2000.

18

Polycystic Ovary Syndrome

- ~8% of reproductive-aged women have polycystic ovary syndrome (PCOS)
- Genetics:

Affected 1st-Degree Relative	Risk of Polycystic Ovary Syndrome (%)
Mother	35
Sister	40

Source: Adapted from Kahsar-Miller MD, Nixon C, Boots LR, et al. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. *Fertil Steril* 75(1):53, 2001.

- Mothers of women with PCOS have elevated low-density lipoprotein/androgen levels as well as markers of insulin resistance (IR) consistent with a heritable trait (Sam 2006).
- PCOS patients frequently develop regular menstrual cycles when aging (Elting 2000), possibly resulting from ↓ size of the follicle cohort? Or from ↓ inhibin?
- **Theory of etiology:** *enhanced serine phosphorylation unification theory* → ↑ CYP17 activity in the ovary (hyperandrogenism) and ↓ insulin receptor activity peripherally (insulin resistance [IR]) (Dunaif 1995) lead to the endocrine dysfunction of PCOS.

CLINICAL SIGNS AND SYMPTOMS

Menstrual Dysfunction

- Onset at menarche: oligo/amenorrhea

19
Female Subfertility

BASIC INFERTILITY

Fast Facts

- 12% of all couples suffer from infertility.
  - Monthly pregnancy rate (PR) in couples with unexplained subfertility after 18 months' duration → 1.5–3.0%
  - Cumulative PRs for couples with unexplained subfertility 1 year and 3 years after the first visit are 13% and 40%, respectively.
- Approximately 50% of healthy women become clinically pregnant during the first two cycles, and between 80% and 90% during the first 6 months (Gnoth 2003; Wang 2003).

DEFINITIONS

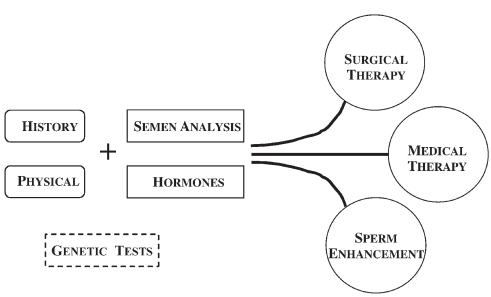
- **Subfertility:** failure to conceive after 1 year of unprotected intercourse (Gnoth 2005)
- **Fecundability:** conception rate; usually *per month*
  - Normal → 20%
  - 38-year-old with 3-year history of infertility → 2%
- **Fecundity:** birth rate per 1 month

20
Male Subfertility

- A male factor is solely responsible in approximately 20% of subfertile couples and contributory in another 30–40%. (Thonneau 1991)
- A history of male fertility is not an accurate predictor of a normal semen analysis (Lucidi 2005).
- Causes of male factor subfertility can be divided into four main categories:
  - Idiopathic (40–50%)
  - Testicular (30–40%)
  - Posttesticular (10–20%)
  - Pretesticular (1–2%)

EVALUATION OF THE MALE PATIENT

- Evaluation of the male should be done before one year of unsuccessful attempts at conception if 1) there are known male infertility risk factors, 2) female infertility risk factors including female age ≥35), 3) the couple questions the male's fertility potential (AUA best practice statement 2010).
- At a minimum, evaluation should include reproductive history and two semen analyses.



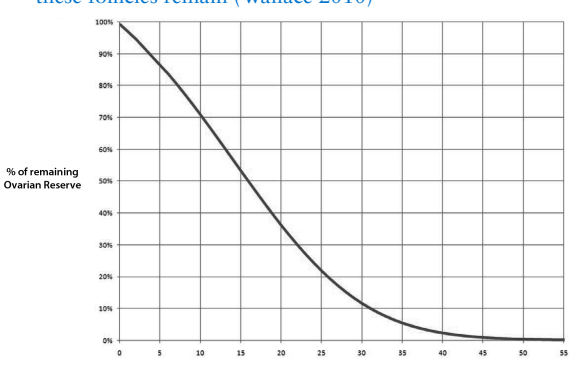
21
Diminished Ovarian Reserve

DEFINITION

- *Diminished ovarian reserve* (DOR) refers to the condition of having a low number of normal oocytes (Scott 1995).

BACKGROUND

- ↑ Age is associated with ↓ fecundity (ability to get pregnant), ↓ live birth rate, ↑ early follicular phase follicular-stimulating hormone (FSH) levels, ↓ anti-müllerian hormone (AMH), ↑ miscarriage rates, and ↑ in vitro fertilization (IVF) cancellation rates due to poor stimulation (Pearlstone 1992; Pellestor 2003; Stein 1985).
- For ~95% of women by the age of 30 years only 12% of their maximum pre-birth non-growing follicles population is present whereas for those at age 40 years only 3% of these follicles remain (Wallace 2010)



Source: Reproduced with permission from Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. *PLoS One*. Jan 27;5(1):e8772, 2010.

22

Assisted Reproductive Technologies

FAST FACTS

- Assisted Reproductive Technologies (ART) by definition are any fertility treatments in which **both egg and sperm** are handled. Accordingly, ART procedures involve the surgical removal of eggs, known as *egg retrieval*.
- In vitro fertilization (IVF) is the most common ART procedure; IVF has been used in the United States since 1980, and data are collected by the Centers for Disease Control and Prevention and published annually (http://www.cdc.gov/art/ARTReports.htm).

DEFINITIONS

- ***In vitro Fertilization*** **(IVF)**: ovulation induction, oocyte retrieval, and fertilization of the oocytes in the laboratory; embryos are then cultured for 3–5 days with subsequent transfer transcervically under abdominal ultrasound guidance into the uterine cavity.
- **Gamete intrafallopian transfer (GIFT)**: ovarian stimulation and egg retrieval along with laparoscopically guided transfer of a mixture of unfertilized eggs and sperm into the fallopian tubes
- **Zygote intrafallopian transfer (ZIFT)**: ovarian stimulation and egg retrieval followed by fertilization of the eggs in the laboratory and laparoscopic transfer of the day 1 fertilized eggs (*zygotes*) into the fallopian tubes
- **Donor egg IVF:** used for patients with poor egg numbers or egg quality; involves stimulation of an egg donor with typical superovulation followed by standard egg retrieval; eggs are then fertilized by the sperm of the infertile woman's

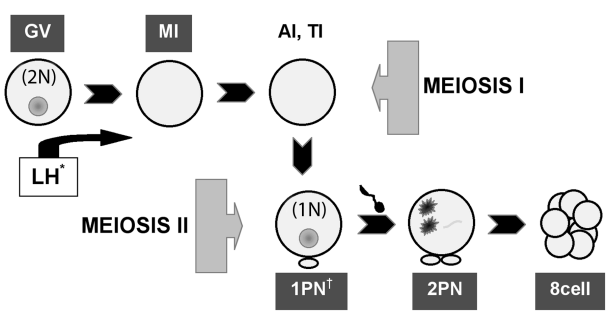
GnRH-agonist utilized (adequate if LH ≥15 mIU/mL and P_4 ≥3 ng/mL).
7. Oocyte retrieval is 36 hours after hCG or GnRH-a.

Natural Cycle IVF

1. Baseline ultrasound between cycle days 2 and 4 of menstrual cycle
2. Monitoring ultrasound on cycle day 7 and serial ultrasounds and E2 levels thereafter
3. When E_2 > 125 pg/mL and follicle >15.5 mm, administer hCG 10,000 U IM.
4. Oocyte retrieval is 36 hours later; aspirate follicle and flush until oocyte is obtained.
   - Benefits to natural cycle IVF:
     - ➔ Lower costs
     - ➔ Elimination of OHSS
     - ➔ Single embryo transfer
     - ➔ Obviates ethical concerns of patients regarding frozen embryos

Oocyte Retrieval

- Typically performed 36 hours after hCG
- Performed under IV sedation using a 5-MHz vaginal transducer with associated needle guide. A 17-gauge, 35-cm aspiration needle is inserted transvaginally into multiple preovulatory follicles with sequential aspiration (low-grade suction <100 mm Hg) of oocytes. The aspirate is then given to the embryologist for evaluation.
- Complications can include intraabdominal bleeding and infection, typically occurring in <1% of IVF cases.



*Arrested at prophase I until luteinizing hormone (LH) surge. †Arrested at metaphase II until fertilization. AI, anaphase I; GV, germinal vesicle; MI, metaphase I; N, nuclei; PN, pronuclei; TI, telophase I.

24

Ovarian Hyperstimulation Syndrome

INCIDENCE

- Iatrogenic complication of superovulation with gonadotropins (rarely clomiphene citrate) with a varied spectrum of clinical and laboratory manifestations
- Incidence in superovulation cycles:
  - Mild ovarian hyperstimulation syndrome (OHSS) → 33%
  - Moderate OHSS → 3–4%
  - Severe OHSS → 0.1–0.2%
- Risk factors:
  - <33 years old
  - Aggressive response to ovarian stimulation (≥18 follicles and/or E_2 ≥5000 ng/dL)
  - Anovulatory women with polycystic ovary syndrome (PCOS)
  - High antral follicle count
  - High basal anti-müllerian hormone (>3.36 ng/mL) (Lee 2008)
  - History of OHSS
  - hCG trigger

CLASSIFICATION

- Clinical, laboratory, and ultrasound findings:
- Symptoms typically start 3–4 days after hCG and peak 7 days after ovulation or follicle aspiration unless patient is pregnant, in which case symptoms persist/worsen.
- Pain is often the first presenting symptom.

26
Gamete Preservation

FEMALE GAMETE PRESERVATION

Medical indications

- Gonadotoxic therapies for cancer and other medical diseases
  - Radiotherapy
  - Autoimmune/collagen vascular disease
  - Oophorectomy for benign/malignant conditions (i.e., endometriosis, ovarian cancer)
- Genetic conditions
  - Women with BRCA mutations may undergo prophylactic oophorectomy
  - Mosaic Turner syndrome (efficacy of oocyte banking unknown)
  - Fragile X permutation (efficacy of oocyte banking unknown)
- Failure to obtain sperm for IVF on day of oocyte retrieval
- Those unable to cryopreserve embryos (moral or religious concerns)
- Elective cryopreservation to defer childbearing

Gonadotoxicity

- Chemotherapy damages the ovaries' steroid-producing cells (granulosa and theca cells) and oocytes → primary ovarian insufficiency (POI) → premature menopause → infertility
  - **Chemotherapy drugs and their potential for gonadal damage: (alkylating agents have the highest risk)**
    1. **High potential: cyclophosphamide (RR between 4-9.3 (Sonmezer and Oktay 2004)), chlorambucil, melphalan, busulfan, nitrogen mustard and procarbazine**
    2. **Moderate potential: cisplatin and adriamycin**

27
Luteal Phase Deficiency

DEFINITION

- Historical definition: >2-day lag in endometrial histologic development (Noyes criteria [Noyes 1950]; updated by Murray 2004)
  - **However, it is no longer recommended to obtain endometrial biopsies, because histologic endometrial dating is neither accurate nor precise** (Murray 2004; Coutifaris 2004).

DIAGNOSIS

- Controversial, ambiguous diagnosis without a definitive diagnostic criteria.
- Consider search for luteal phase deficiency (LPD) if:
  - Normal cycles and unexplained infertility
  - >35 years old
  - Short luteal phases (<13 days from positive LH peak to menses)
  - History of recurrent losses (28% associated with LPD) (Vanrell and Balasch 1986).

INCIDENCE

- Perhaps 30% of isolated cycles in fertile women; 30–40% of infertile women

ETIOLOGY

- Plausible etiologies:
  - ↓ Hormone production by corpus luteum
  - ↓ Follicle-stimulating hormone (FSH) in follicular phase (FSH stimulates granulosa cell proliferation and luteinizing hormone [LH] receptors on granulosa cells)

28

Hyperprolactinemia and Galactorrhea

DEFINITION

- Consistently elevated fasting serum prolactin in the absence of pregnancy or postpartum lactation; nonpuerperal lactation

PROLACTIN

- Little PRL = polypeptide hormone of 198 amino acids, but there are several different circulating forms:
- Circulating big PRL can be converted to little PRL by disulfide bond reduction
- In the vast majority of cases, big-big PRL (bbPRL) consists of a complex of PRL and an anti-PRL IgG autoantibody and is referred to as macroprolactin. Less commonly, big-big PRL is composed of either covalent or noncovalent polymers of monomeric PRL. This may account for 10% of hyperprolactinemia but this is not symptomatic (Gibney 2005).
- Macroprolactin (or bbPRL) should be suspected when the clinical history or MRI findings are inconsistent with the elevated PRL (D'Ercole 2010).

Name	Molecular Weight	Biologically Active	Immunologically Active
Little PRL	22 kd	Yes	Yes
Glycosylated little PRL	25 kd	Yes, but decreased	No
Big PRL	50 kd	No	Yes
Big-big PRL	>100 kd	No	Yes

PRL, prolactin.

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Hypothyroidism

PREVALENCE

- ↑ Thyroid-stimulating hormone (TSH) is found in 4–10% of all adult women (Hollowell 2002).

THYROID FUNCTION

- Most of the released hormone is thyroxine (T_4), which is then peripherally converted to triiodothyronine (T_3).
- T_3 is more biologically active than T_4.

SIGNS AND SYMPTOMS

- Fatigue
- Dry or rough skin
- Irritability
- Weakness
- Hair loss
- Myalgia
- Memory loss
- Weight gain
- Cold intolerance
- Constipation
- Abnormal menses
- Coarse or dry hair
- Depression
- ↓ Libido
- Primary thyroid failure → abnormal uterine bleeding
- Hyperthyroidism → oligomenorrhea

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Recurrent Pregnancy Loss

FAST FACTS

- Fetal viability is only achieved in 30% of all human conceptions, 50% of which are lost before the first missed menses (Edmonds 1982).
- **15–20%** of clinically diagnosed pregnancies are lost in the 1st or early 2nd trimester (TM) (Warburton and Fraser 1964; Alberman 1988).
- Risk of loss:
  - 12% after one successful pregnancy
  - 24% after two consecutive losses
  - 30% after three consecutive losses
  - 40% after four consecutive losses
- Risk of a 4th loss after three prior losses depends on past reproductive history:
  - If no prior live birth → 40–45%
  - If ≥1 prior live birth → 30%
- ↑ Rate of pregnancy loss with advanced maternal age (most common cause is isolated nondisjunction)

Incidence of SM or RM Occurring by Chance and of RM in Total, in Women of Different Age Groups

Age Groups (years)	Sporadic Miscarriage (%)[a]	Rm Occurring by Chance[b], % (CI)	RM Occurring in Total (%)
20–24	11	0.13 (0.13–.013)	-
25–29	12	0.17 (0.17–0.17)	~0.4
30–34	15	0.34 (0.34–0.34)	~1
35–39	25	1.56 (1.56–1.56)	~3
40–44	51	13.3 (13.29–13.31)	-

CI, confidence intervals for binomial proportions.
[a]Data from Nybo Anderson et al. (2000).
[b]Calculated based on the assumption that if sporadic miscarriage rate = μ, recurrent miscarriage rate occurring by chance = μ^3

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Management of Early Pregnancy Failure

- **Early pregnancy failure (EPF):** broader term describing 1st trimester pregnancy failures; preferred term by many
- Incidence of pregnancy loss:
  - 15–20% of all clinically diagnosed pregnancies
  - Mortality for spontaneous abortions: approximately 0.4 in 100,000 (Creinin 2001)
  - If bleeding occurs before 6 weeks of gestation, there is no increase in adverse pregnancy outcomes; bleeding >7 weeks, even with cardiac activity, indicates a risk for pregnancy loss ~10% as opposed to 5% if there is no bleeding (Jauniaux 2005; Juliano 2008).

DEFINITIONS

Anembryonic pregnancy: Double decidual sign sac without an embryo

Blighted ovum: literally "bad egg"; often used to mean *anembryonic pregnancy* but not currently the preferred terminology

Embryonic demise: demise of an embryo between 4 and 15 mm in length; lack of cardiac activity documented by ultrasound

Fetal demise: demise of a fetus >15 mm in crown-rump length; lack of cardiac activity documented by ultrasound

Incomplete abortion: passage of some but not all fetal or placental tissue <20 weeks gestation

Inevitable abortion: uterine bleeding at gestational age <20 weeks, with cervical dilation but without passage of any fetal or placental tissue

Threatened abortion: uterine bleeding at <20 weeks gestation, without cervical dilation or effacement

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Primary Ovarian Insufficiency/Primary Ovarian Failure

DEFINITION *(Rebar and Connolly 1990)*

- <40 years old
- Follicle stimulating hormone (FSH) > 30 mIU/mL × 2 at least 1 month apart
  - E_2 < 50 pg/mL signifies nonfunctioning follicles
- Amenorrhea ≥4 months*
  *more likely there is > 4 months of disordered menses (amenorrhea, oligomenorrhea, polymenorrhea, metrorrhagia) (Nelson 2009)

- Primary ovarian insufficiency (POI) = hypergonadotropic amenorrhea
- Oocyte physiology: The acme in number of oocytes is reached by 20 weeks of gestation when the number reaches 6 million. By birth, this number is down to 2 million, and approximately 400,000 follicles are present at the onset of puberty. Through the process of apoptosis, no responsive oocytes are found by the time of menopause. The timing of ovarian failure is determined by both the original oocyte quantity and the rate of apoptosis.
- The above dogma has recently been challenged by data indicating the presence of **germ stem cells** in ovaries (White 2012).

INCIDENCE *(Coulam 1986; Luborsky 2003)*

- **1.1%**
  - 0.1% by age 30 years
  - 1.1% by age 40 years
  - 10–28% of those with primary amenorrhea

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Genetic Testing

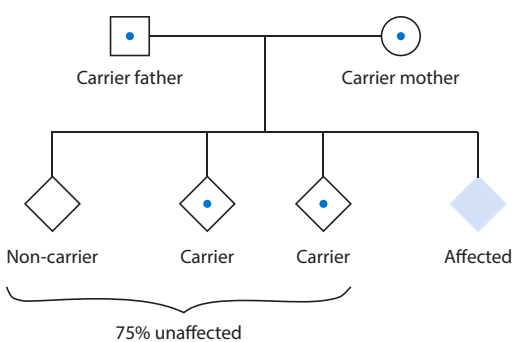
There are many genetic screening tests that may be appropriate for couples considering pregnancy. These include: carrier screening, diagnostic testing for male factor (Y chromosome microdeletion) and female factor infertility (Turner syndrome, fragile X syndrome), and testing during pregnancy for high-risk aneuploidies.

CARRIER SCREENING

- Testing to identify individuals/couples at risk to have a child with a genetic disorder.
- Typically ordered based on ethnic background, prior affected child and/or family history.
- Based on results of genetic testing, patients should be offered genetic counseling to discuss their reproductive risks and options.

Autosomal Recessive Inheritance

- Most disorders screened are autosomal recessive. Two carriers of the same disorder have a 25% risk with each pregnancy to have an affected child.



- Especially useful for individuals with mixed ethnicity or those unaware of their ethnicity

Disorder (*Gene*)	Ethnicity	Carrier frequency	Recommendation
Cystic fibrosis (*CFTR*)	African American Ashkenazi Jewish Asian Caucasian Hispanic	1 in 61 1 in 23 1 in 94 1 in 25 1 in 58	ACOG & ACMG: recommended for **all women of reproductive age**, regardless of ethnic background
Fragile X syndrome (*FMR1*)	All ethnicities	1 in 178 women	Recommended based on medical and/or family history
Spinal muscular atrophy (*SMN1*)	African American Ashkenazi Jewish Asian Caucasian Hispanic	1 in 72 1 in 67 1 in 59 1 in 47 1 in 68	ACMG: recommended for **all women of reproductive age**, regardless of ethnic background

- **Cystic fibrosis (CF)**: an **autosomal recessive**, chronic disorder affecting epithelia of the respiratory, gastrointestinal, genitourinary, and hepatobiliary systems. Symptoms include but are not limited to: obstructive lung disease, recurrent lung infection, meconium ileus, pancreatic insufficiency, recurrent pancreatitis, malnutrition, and male infertility. In severe cases, lung transplant may be necessary; pulmonary disease is the major cause of mortality. Average lifespan is into the late 30's.
  - Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) on chromosome 7 encodes a chloride channel in the epithelia.
    - ➔ >1900 known variants reported in *CFTR* (Cystic Fibrosis Mutation Database http://www.genet.sickkids.on.ca). Not all are pathogenic.
  - Incidence in the United States: ~1/3,700, regardless of gender; varies by ethnic background (see carrier frequencies above) (CDC and Prevention 2004)
  - Genitourinary symptom include male infertility, specifically congenital bilateral absence of the vas deferens (CBAVD), presenting as **obstructive azoospermia** (see Male Subfertility, p. 240).

Two Copies of *SMN1*
Normal carrier screening result
• increased risk to have an affected child

❖ 3 copies: reduced residual risk

Three Copies of *SMN1*
Normal carrier screening result
• very reduced risk to have an affected child

- **Routine carrier screening for SMA:** copy number analysis of *SMN1*.
  - ➔ Copy number of *SMN1* (determined by the copy number of exon 7) is done by a PCR-based assay, such as multiplex ligation-dependent probe amplification (MLPA).

Ethnic-Specific Carrier Screening

Disorders typically recommended based on a patient's ethnic background. Disorders may occur outside of high-risk ethnicities.

Ethnic Background	Disorder	Carrier Frequency
African American	Alpha thalassemia Beta thalassemia Sickle cell disease	1 in 30 1 in 75 1 in 10
Ashkenazi Jewish	Ashkenazi Jewish panel*	1 in 5
Asian	Alpha thalassemia Beta thalassemia	1 in 20 1 in 50
Cajun	Tay-Sachs disease	Increased
French Canadian	Tay-Sachs disease	1 in 251
Irish	Tay-Sachs disease	1 in 522, 3
Hispanic	Alpha thalassemia Beta thalassemia Sickle cell	Variable 1 in 32–75 1 in 30–200
Mediterranean	Alpha thalassemia Beta thalassemia Sickle cell disease	1 in 30–50 1 in 20–30 1 in 30–50
Middle Eastern	Alpha thalassemia Beta thalassemia Sickle cell disease	Variable 1 in 50 1 in 50–100
Sephardic Jewish	Alpha thalassemia Beta thalassemia Sephardic Jewish panel**	1 in 4–100 1 in 5–7 Increased

[1]Andermann 1977. [2]Van Bael 1996 [3]Branda 2004

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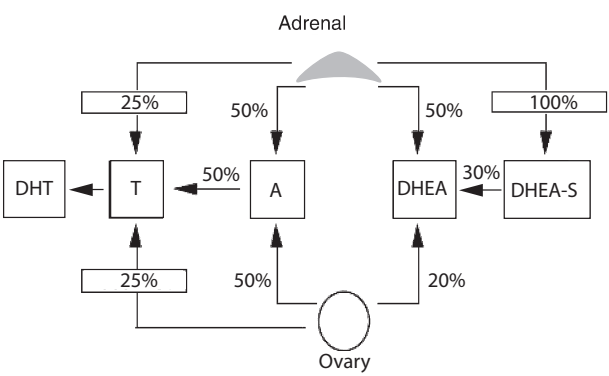
Androgen Replacement Therapy

ANDROGENS

- The majority of androgens are synthesized by the adrenal glands and ovaries:
  - Pro-hormones: A, androstenedione; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate
  - Potent androgens: T, testosterone and the non-aromatizable dihydrotestosterone (DHT)



Source: Adapted from Fritz MA, Speroff L. Normal and Abnormal Growth and Pubertal Development. In: *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2011.

- Relative binding affinity of hormones to sex hormone–binding globulin (SHBG): DHT > testosterone (T) > androstenedione (A) > estradiol (E_2) > estrone (E_1) (Dunn 1981). Only free (i.e., unbound to SHBG) hormones are

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Postmenopausal Hormone Therapy

HORMONE REPLACEMENT THERAPY (1950s–1990s) → HORMONE THERAPY (2002 TO PRESENT)

- Although the Women's Health Initiative (WHI) estradiol (E_2)/progestin and estrogen-only studies (see Hormone Therapy Risks and Benefits section) are not perfect, the indications and duration of hormone therapy (HT) have been revised.
- Many areas are still controversial; the following are general recommendations:
- **Risks** and **benefits** of these interventions for perimenopausal and naturally and surgically postmenopausal women are now more clearly defined.
  - Unopposed estrogen therapy **does not ↑ breast cancer incidence** (see WHI data below); the role of progestins in combined E_2 /progestin HT is still controversial.
  - While much data exists on **prevention and treatment of osteoporosis** (with fracture outcomes and bone mineral density [BMD]), estrogen therapy is an option but no longer recommended as first line therapy given the long-term risks associated with treatment (e.g., stroke, VTE). Raloxifene or bisphosphonates are preferred.
  - HT for primary prevention of coronary heart disease (CHD) is no longer recommended; current data suggest that **neither primary nor secondary prevention of CHD is a valid indication** for starting or continuing therapy.
  - Major indications for systemic HT with estrogen ± progestin are relief of **menopausal symptoms** and **prevention of osteoporosis.**

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Hot Flashes

INCIDENCE

- Overall incidence:
  - Premenopausal: 25%
  - Late perimenopausal: 69%
  - Late postmenopause: 39%

BACKGROUND

- Usually a sensation of heat, sweating, flushing, dizziness, palpitations, irritability, anxiety, and/or panic
- Classic hot flash (HF): head-to-toe sensation of heat, culminating in perspiration
- Large cross-cultural variability in prevalence:

%	Culture
0	Mayan women in Mexico
18	Chinese factory workers in Hong Kong
70	North American women (black women > white women)
80	Dutch women

- Despite these vast differences, some trends are seen:
  - HFs usually last 0.5–5.0 years (but may last up to 15 years); one study reported that among women who had experienced moderate to severe HFs, 58% persisted at 5 years, 12% at 8 years, and 10% at 15 years subsequent to reaching menopause.

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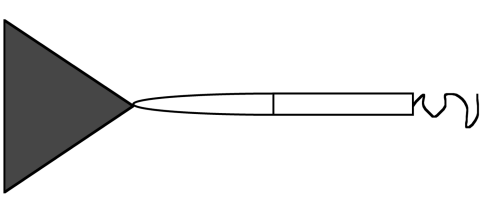
Transvaginal Ultrasound in Reproductive Endocrinology and Infertility

BASIC PRINCIPLES OF SCANNING

- Develop a routine to systematically scan all pelvic structures.
- Each structure must be scanned in two planes perpendicular to one another.
- Transducer's position should be monitored during insertion. Once the probe has been properly inserted, the operator should observe the screen at all times, and the position of the probe is determined by optimal visualization of the pelvic viscera. The orientation of the probe is controlled by angulation (accomplished by up and down movement of the transducer handle) and rotation:
  - The probe can be rotated 90 degrees around its axis to obtain sagittal and coronal plane images.
  - The probe can be angled in any plane to direct the plane of image.
  - Deeper insertion or withdrawal can be used to bring the area of interest within the focal zone of the transducer.
- The scan area needs to be thought of as a pie-shaped area emanating from the transducer:



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Hysteroscopy

RESECTOSCOPE HYSTEROSCOPY SETTINGS

Electrode	Current	Watts
VaporTrode (all three types)	Pure cut	200
	Coag	75
Loop	Pure cut	90–120
	Coag	75
Roller ball coag	Pure cut	100–200
	Coag	75

Coag, coagulation.

- Hysteroscopic myomectomy resection: Use VaporTrode cutting and, to clean instrument head, use coagulation setting.

PRESSURE AND POSITIONING

- 40–50 mm Hg to open the uterine cavity (Baker and Adamson 1998)
- 70–75 mm Hg usually adequate for surgery
- Set pump pressure at the patient's mean arterial pressure (MAP); ask anesthesiologists for the patient's MAP; for every foot above the uterus → 10 mm Hg.
- Maximum doses of lidocaine for 60-kg woman: 270 mg (or 27 mL 1% solution) (without epinephrine), 420 mg (with epinephrine) (or 42mL 1% solution)
- Buccal or sublingual misoprostol (200–400 μg) the night before surgery may help dilate the cervix.

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Laparoscopy

PATIENT PREPARATION AND POSITIONING

Bowel Preparation

- Types: Fleets Phosphosoda, magnesium citrate, GoLYTELY
- Extrapolating from the general surgery literature (Contant 2007), it is reasonable to omit mechanical bowel preparation (which does seem to contradict existing dogma) (Cohen 2011).

Histamine Receptor Blockade

- Recommended for obese patients: ranitidine 50 mg IV 20 minutes prior to surgery.

Positioning

- Modified lithotomy:
  - Hips slightly flexed and thighs parallel to the abdomen; this facilitates access to upper pelvic/abdominal structures and tissue removal.
  - Make sure legs are well positioned and protected (see Positioning Injuries below).
  - Anti-skid material under thorax
  - Sequential compression devices for the lower extremities
- Sacrum: Avoid undue pressure leading to coccydynia.
- Foley catheter for bladder decompression and proper placement of suprapubic port
- Arms adducted and pronated to side and tucked to the patient's side
  - Protect fingers, hands, and elbows with foam cushions.
- Patient supine (0 degrees) for initial Veress needle insertion and primary trocar
- Steep Trendelenburg (20–30 degrees) during the case

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Journal Club Guide

REFERENCE

- Title of article, authors, journal, site(s) of research

BACKGROUND INFORMATION ON THE TOPIC

- Review of the literature suggesting the purpose of the article and how it contributes to the field of knowledge in the specific area

HYPOTHESIS

- Research question (explicitly stated or implied)
- To what population will the findings apply? (relevance of the study)

METHODS/STUDY DESIGN

- Type of study (i.e., descriptive, cross-sectional, cohort, case-control, randomized controlled trial [RCT], meta-analysis, and so forth)
- Selection of study subjects (i.e., How were the subjects chosen? Are there any potential sources of bias? Were the groups similar at the start of the trial? Confounding variables can be controlled for in an RCT [e.g., stratification].)
- Were patients, health workers, and study personnel "blind" to treatment?
- Inclusion/exclusion criteria
- Bias that may have been introduced (ascertainment bias? what was exposure?)
- Control subjects
- IRB approval and clinicaltrials.gov registration (if a clinical trial).

Chapter Key Points

SEXUAL DIFFERENTIATION

- Imperforate hymen and transverse vaginal septum can be difficult to differentiate and are associated with other GU and bony abnormalities. MRI can be useful in the pre-operative evaluation.
- Patients with Congenital Adrenal Hyperplasia require corticosteroids. During childhood, growth curves are one of the most sensitive ways to follow them—if they are over-replaced, the growth curve will taper.
- Timing of gonadectomy in CAIS is controversial, with some recommendations favoring post pubertal gonadectomy to permit normal breast development and pubertal growth, and others cautioning against the age-related risk of gonadoblastoma.
- Male reproductive development requires an active process. The 'default' reproductive phenotype is female (although not necessarily a gonadally competent female). A testis determining factor must be produced and female reproductive organ development must be suppressed.
- Y chromosome containing gonadal tissue should NOT reside in the abdominal cavity!—gonadectomy should be performed—timing depends upon exact defect, always before age 30.
- Genitoplasty guidelines are evolving, trend is to wait until adolescence if parents and child can tolerate ambiguity.
- Most common primary amenorrhea genetic disorders are Turner Syndrome (1/2500) and Mullerian Agenesis (1/4000–1/10,000).

PUBERTY

- Although the median age at onset of puberty and menarche has grown earlier over the past century, the median age at menopause has remained the same.